THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Pasricha, P.J.	§	**ART UNIT:**
	§	**1617**
FILED: September 19, 2003	§	
	§	**EXAMINER:**
SERIAL NO.: 10/665,770	§	**Kim, Jennifer M.**
	§	
FOR: Treatment of Irritable Bowel Syndrome and Related Bowel Diseases	§	**DOCKET:**
	§	**D6475**

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P.O. Box 1450
Alexandria, VA 22313

ATTENTION: Board of Patent Appeals and Interferences

APPEAL BRIEF

This Appeal Brief is in furtherance of the Notice of Appeal transmitted via facsimile in this case on May 26, 2009. The fees required under 37 C.F.R. §41.20(b)(2) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF. However, if this is in error, please debit any additional fees due from Deposit Account No. 07-1185 on which Applicant's counsel is allowed to draw.

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Respectfully submitted,

Date: August 20, 2009

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INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is The Board of Regents of the University of Texas System.

II. RELATED APPEALS AND INTERFERENCES

Appellant is aware of no related appeals and interferences of the present invention.

III. STATUS OF CLAIMS

Originally, claims 1-18 were filed and being prosecuted in this application. Claims 7-9 and 16-18 are withdrawn from consideration. Of the pending claims 1-6 and 10-15, claims 1 and 10 are independent.

IV. STATUS OF AMENDMENTS

In response to an Office Action, claims 1 and 10 were amended. In Response to a Final Office Action mailed January 23, 2009, a Notice of Appeal was filed on May 26, 2009 appealing the rejection of the pending claims 1-6 and 10-15 as shown in the Claims Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of independent claim 1 is drawn to a method of treating an individual having irritable bowel syndrome (pg. 16, lines 3-6). The step involves administering to the individual an effective dose of luminally active anti-inflammatory compound with minimal or no systemic side effects. These compounds include steroids such as beclomethasone which are minimally absorbed and budesonide which though absorbed, undergo extensive first pass metabolism in the liver and do not exert significant systemic effects (pg 16, lines 7-16).

The subject matter of independent claim 10 is drawn to a method of alleviating the symptoms of irritable bowel syndrome in an individual. The step involves administering to the individual an effective dose of a luminally active anti-inflammatory compound with minimal or no systemic side effects such that the administration increases the threshold of pain to colorectal distention, thereby alleviating the symptoms of irritable bowel syndrome (pg 21, lines 5-14; Fig 2).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 10-14 are anticipated by **Chiesi** *et al.*, (WO 00/06132A2) as is evidenced by **Basu** *et al.* (US 2002/0025348A1) under 35 U.S.C. §102(b).

Whether claims 1-6 and 15 are obvious over **Chiesi** *et al.* (WO 00/06132A2) in view of **Basu** et al. (US 2002/0025348A1) under 35 U.S.C. §103(a).

VII. ARGUMENT

Rejection of Claims 10-14 under 35 U.S.C. §102(b) over by **Chiesi** et al., (WO 00/06132A2) as is evidenced by **Basu** et al

It is well established that in order to anticipate a claim under 35 U.S.C. §102(b), each and every element of the claim should be described in a single prior art reference, either expressly or inherently. Importantly, the identical invention must be shown in as complete detail as is contained in the instant invention. Applicants' claim 10 is directed towards to a method of alleviating the symptoms of irritable bowel syndrome in an individual. The step involves administering to the individual an effective dose of a luminally active anti-inflammatory compound with minimal or no systemic side effects such that the administration increases the threshold of pain to colorectal distention, thereby alleviating the symptoms of irritable bowel syndrome (IBS).

Applicants respectfully submit that **Chiesi** *et al.* as evidenced by **Basu** *et al.* do not teach a method of alleviating the symptoms of irritable bowel syndrome, as recited in Applicants' claim 10. **Chiesi** *et al.* is directed to the treatment of inflammatory bowel disease (IBD). There is no explicit teaching in **Chiesi** *et al.* regarding the treatment of irritable bowel syndrome. The Examiner argues that this lack of teaching is overcome by **Basu** *et al.* which disclose that irritable bowel syndrome also tends to occur in inflammatory bowel disease patients who are in remission from their inflammatory bowel disease symptomologies.

The Applicants respectfully submit that even if a certain population of patients suffering from irritable bowel syndrome may overlap with patients suffering from inflammatory bowel disease, the two disorders have been regarded as separate disorders, requiring separate pharmacotherapies. Even if inflammation may exist in irritable bowel syndrome, it is different than a typical inflammatory bowel disease such as ulcerative colitis or Crohn's disease for several reasons. First, there is no evidence of tissue injury or destruction either at the macroscopic or microscopic level. Second, the major cell types that appear to be affected in irritable bowel syndrome are the muscle and nerves as compared to inflammatory bowel disease, where the epithelium is the prominent major target. Therefore, even if immunocompetent cells are contributing to the pathogenesis of irritable bowel syndrome, they might be doing so by means that are not intuitively obvious and may involve different mechanisms than those in inflammatory bowel disease. Thus, the treatments claimed in the instant invention are novel at least in part because they involve the use an anti-inflammatory compound in the treatment of a disorder that is not considered an inflammatory disorder.

As supplementary evidence, Applicants have argued that the prior art considers irritable bowel syndrome and inflammatory bowel disease to be separate and distinct disorders. For example, Applicant submitted **Quigley** *et al.* which point out that despite some studies suggesting otherwise, any convergence of irritable bowel syndrome and inflammatory bowel disease is largely due to misdiagnosis (Quigley, Chin J Dig Dis. 2005; 6(3):122-132).

The National Institute of Health also has regarded irritable bowel syndrome and inflammatory bowel disease to be wholly unrelated disorders: "[t]hrough

the years, irritable bowel syndrome has been called by many names, among them colitis, mucous colitis, spastic colon, or spastic bowel. However, no link has been established between irritable bowel syndrome and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis." (http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/#what)

In addition, the Crohn's and Colitis Foundation of America has stated that "[t]hrough the years, irritable bowel syndrome has been called by many names, among them colitis, mucous colitis, spastic colon, or spastic bowel. However, no link has been established between irritable bowel syndrome and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis." (http://www.ccfa.org/about/news/ibsoribd)

The Applicants have further submitted as evidence published at the time of filing of the invention that chronic inflammatory mucosal changes in the gut are not a plausible mechanism to explain the presence of chronic abdominal pain, which is a cardinal irritable bowel syndrome symptom (**Schwetz** et al., Curr Gastroenterol Rep. 2003 Aug; 5(4): 331-336). Therefore, given the state of art at the time of filing of the instant invention, a person having ordinary skill in this art would not consider patients with inflammatory bowel disease to be patients that need treatment for irritable bowel syndrome.

Furthermore, irritable bowel syndrome is considered a functional bowel disorder while inflammatory bowel disease is characterized by organic changes such as inflammation or ulceration in the small and/or large intestines. At least one symptom criteria (Rome criteria) states that once organic changes are detected, a diagnosis of functional disorder cannot be made. Thus, irritable bowel syndrome and inflammatory

bowel disease are distinct disorders and a person having ordinary skill in this art would not attempt to treat patients with inflammatory bowel disease for irritable bowel syndrome.

Additionally, the Applicants submit that **Basu** *et al.* suggest that inflammatory bowel disease and irritable bowel syndrome are separate disorders as evidenced by the claim construction in **Basu** et al. For example, claim 9 is directed to a method for treating a bowel disorder where the bowel disorder is inflammatory bowel disease. In contrast, claim 10 is directed to a method for treating a bowel disorder where the bowel disorder is irritable bowel syndrome. Thus, **Basu** *et al.* obviously considered inflammatory bowel disease and irritable bowel syndrome to be separate and distinct diseases.

Furthermore, even assuming *arguendo* that there is substantial overlap in a population of patients suffering from inflammatory bowel disease with patients suffering from irritable bowel syndrome, there is no disclosure in **Chiesi** *et al.* or **Basu** *et al.* which suggests that anti-inflammatory agents may be used to treat irritable bowel syndrome. Thus, **Chiesi** *et al.* as is evidenced by **Basu** *et al.* would not enable a person of ordinary skill in this art to make and use the invention given that irritable bowel syndrome and inflammatory bowel disease are unrelated disorders.

For these reasons, Applicants submit that claims 10-14 are not anticipated under 35 U.S.C. §102(b) by **Chiesi** *et al.* as evidenced by **Basu** *et al.* Accordingly, Applicants respectfully request the Board of Patent Appeals and Interferences to reverse the rejection of claims 10-14 under 35 U.S.C. §102(b).

Rejection of Claims 1-6 and 15 under 35 U.S.C. §103 over **Chiesi** *et al.* (WO 00/06132A2) in view of **Basu** *et al.* (US 2002/0025348A1)

Applicant's claim 1 is directed to a method of treating an individual having irritable bowel syndrome. The step involves administering to the individual an effective dose of luminally active anti-inflammatory compound with minimal or no systemic side effects. Applicant's claim 15 is directed towards to a method of alleviating the symptoms of irritable bowel syndrome in an individual. The step involves administering to the individual a certain dose of orBecTM, thereby alleviating the symptoms of irritable bowel syndrome.

Applicants respectfully submit that **Chiesi** *et al.* as evidenced by **Basu** *et al.* do not teach a method of treating an individual having irritable bowel syndrome, as recited in claim 1. **Chiesi** *et al.* is directed to the treatment of inflammatory bowel disease. There is no explicit teaching in **Chiesi** *et al.* regarding the treatment of irritable bowel syndrome. The Examiner argues that this lack of teaching is overcome by **Basu** *et al.* which state that irritable bowel syndrome may be related to inflammatory bowel disease.

The Applicants submit that at the time of the invention, there is strong support that irritable bowel syndrome and inflammatory bowel disease have disparate pathophysiologies and thus require different pharmacotherapies. As discussed *supra*, the Applicants have submitted as corroborative evidence: **Quigley** *et al.*, **Schwetz** *et al.*, and statements from the National Institute of Health and Crohn's and Colitis Foundation of America websites.

In addition, **Basu** *et al.* state that there is no satisfactory explanation regarding the pathophysiology of irritable bowel syndrome. **Basu** *et al.* never explicitly state that one of the symptoms of irritable bowel syndrome is inflammation, only that irritable bowel syndrome and inflammatory bowel disease are related disorders. Although inflammatory bowel disease is usually classified as ulcerative colitis or Crohn's disease, it also includes forms of microscopic colitis, e.g. histologic evidence of mucosal inflammation without macroscopic abnormalities. Inflammatory bowel disease is characterized by a constellation of patient-reported history and endoscopic, histopathologic and radiologic findings often with serologic correlations. Classic signs that reflect the inflammatory process within the gastrointestinal tract are rectal bleeding, diarrhea, fever and weight loss occasionally associated with extraintestinal manifestations.

In contrast, irritable bowel syndrome is classified as functional bowel disorder and is traditionally diagnosed on the basis of a characteristic cluster of symptoms in the absence of detectable structural abnormalities. According to the symptom criteria (Rome criteria), once organic changes are detected, a diagnosis of functional disorder cannot be made. Theories which aim to explain the pathophysiology of irritable bowel syndrome include alteration in the visceral perception, gastrointestinal motility and gut epithelia and immune function. Considerable evidence supports the role of psychosocial and physical stressors as central and peripheral triggers respectively of first symptom onset of exacerbation. Although there is considerable interest in the putative role of low-grade chronic inflammation in the pathogenesis of irritable bowel syndrome, enhanced

responsiveness to psychosocial and physical stressors has been suggested as a plausible mechanism that could explain most clinical and experimental findings in irritable bowel syndrome. Thus, there is ample scientific evidence demonstrating that irritable bowel syndrome and inflammatory bowel disease are distinct diseases. The Examiner, in distinct contrast, has produced no scientific evidence to the contrary.

Furthermore, Applicants respectfully point to the NIH website which states that bleeding, fever, weight loss and persistent severe pain are **not** symptoms of irritable bowel syndrome and may indicate other problems such as inflammation or rarely, cancer. In other words, one cannot categorize irritable bowel syndrome to be an inflammatory disorder. Thus, a person having ordinary skill in this art would not consider both irritable bowel syndrome and inflammatory bowel disease to be inflammatory diseases. Additionally, the Examiner's statement that irritable bowel syndrome tends to occur in inflammatory bowel disease patients who are in remission from their inflammatory bowel disease symptomologies also would lead one not to speculate that inflammation is involved in the occurrence of irritable bowel syndrome because if the inflammation persisted, then the patient would still be diagnosed as having inflammatory bowel disease and not irritable bowel syndrome.

The last paragraph on page 13 of the instant specification discusses how the inflammation if present, in irritable bowel syndrome is different from inflammatory bowel disease and may involve mechanisms that are different from inflammatory bowel disease in contributing to the pathogenesis of irritable bowel syndrome. Applicants also provide a report that was published at the time of filing of the instant invention, which teaches that chronic inflammatory mucosal changes in the gut is not a plausible

mechanism to explain the presence of chronic abdominal pain, a cardinal irritable bowel syndrome symptom (**Schwetz** *et al.*, Curr Gastroenterol Rep. 2003 Aug; 5(4): 331-336). Hence, one of skill in the art would not be motivated to use an anti-inflammatory agent to treat irritable bowel syndrome.

Even if one of skill in the art were motivated to use an anti-inflammatory agent based on teachings of **Basu** *et al.*, there would be no reasonable expectation in treating irritable bowel syndrome based on the report discussed *supra* and since neither **Chiesi** *et al.* nor **Basu** *et al.* demonstrate that the anti-inflammatory agent was successful in treating irritable bowel syndrome or the symptoms of irritable bowel syndrome discussed herein.

Accordingly, Applicants respectfully request that the Board of Patent Appeals and Interferences reverses the rejection of claims 1-6 and 15 under 35 U.S.C. §103.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

Claim 1 (previously presented): A method of treating an individual having irritable bowel syndrome, comprising the step of:

administering to said individual a pharmacologically effective dose of a luminally active anti-inflammatory compound with minimal or no systemic side effects.

Claim 2 (original): The method of claim 1, wherein said luminally active anti-inflammatory compound is a steroid.

Claim 3 (original): The method of claim 2, wherein said steroid is beclomethasone.

Claim 4 (original): The method of claim 3, wherein said beclomethasone is beclomethasone dipropionate.

Claim 5 (original): The method of claim 4, wherein said beclomethasone dipropionate is orBecTM.

Claim 6 (original): The method of claim 4, wherein said orBecTM is administered in a dose of from about 0.1 mg/kg to about 20 mg/kg.

Claim 7 (withdrawn): The method of claim 1, wherein said anti-inflammatory compound is budesonide, clobetasol, halbetasol, fluocinonide, halcinonide, betamethasone, mometisone, alclometasone, triamcinolone or fluocinolone.

Claim 8 (withdrawn): The method of claim 1, wherein said immunosuppressive compound is selected from the group consisting of methotrexate, azothiorpine, 6 mercaptopurine, cyclosporine and FK506.

Claim 9 (withdrawn): The method of claim 1, wherein said a related disorder is non-ulcer dyspepsia or noncardiac chest pain.

Claim 10 (previously presented): A method of alleviating the symptoms of irritable bowel syndrome in an individual in need of such treatment, comprising the step of:

administering to the individual a pharmacologically effective dose of a luminally active anti-inflammatory with minimal or no systemic side effects such that said administration increases the threshold of pain to colorectal distention, thereby alleviating the symptoms of irritable bowel syndrome in the individual.

Claim 11 (original): The method of claim 10, wherein said luminally active anti-inflammatory compound is a steroid.

Claim 12 (original): The method of claim 11, wherein said steroid is beclomethasone.

Claim 13 (original): The method of claim 12, wherein said beclomethasone is beclomethasone dipropionate.

Claim 14 (original): The method of claim 13, wherein said beclomethasone dipropionate is orBecTM.

Claim 15 (original): The method of claim 14, wherein said orBecTM is administered in a dose of from about 0.1 mg/kg to about 20 mg/kg.

Claim 16 (withdrawn): The method of claim 10, wherein said luminally active anti-inflammatory compound is budesonide.

Claim 17 (withdrawn): The method of claim 10, wherein said immunosuppressive compound is methotrexate, azothiorpine, 6 mercaptopurine, cyclosporine and FK506.

Claim 18 (withdrawn): The method of claim 1, wherein said a related disorder is non-ulcer dyspepsia or noncardiac chest pain.

IX. EVIDENCE APPENDIX

Schwetz *et al.*, Curr Gastroenterol Rep. 2003 Aug; 5(4): 331-336 was entered into the record after filing the response to Final Office Action, submitted February 8, 2008.

The NIH website information was entered into the record after filing the response to Final Office Action, submitted February 8, 2008.

Quigley, Chin J Dig Dis. 2005; 6(3):122-132 was entered into the record after filing the response to Final Office Action, submitted April 21, 2009.

The Crohn's and Colitis Foundation of America website information was entered into the record after filing the response to Final Office Action, submitted April 21, 2009.

1: Curr Gastroenterol Rep. 2003 Aug;5(4):331-6.

Links

Current insights into the pathophysiology of irritable bowel syndrome.

Schwetz I, **Bradesi S**, **Mayer EA**.

Center of Neurovisceral Sciences and Women's Health, CURE: Digestive Diseases Research Center, David Geffen School of Medicine at UCLA, VAGLAHS, Bldg. 115, Room 223, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA. emayer@ucla.edu

Recent reports have emphasized the possible role of mucosal immune activation and inflammation in neuropathic changes in the pathophysiology of irritable bowel syndrome (IBS). However, novel findings using functional brain imaging techniques have underlined the importance of altered perception of visceral stimuli to symptom generation in IBS. These new developments have rekindled an old debate on peripheral versus central mechanisms in the pathophysiology of IBS. In this review we discuss the latest findings in light of these two concepts. In addition, we provide evidence for the hypothesis that, in the absence of alterations in endogenous pain modulation systems and changes in visceral perception, chronic inflammatory mucosal changes in the gut are not a plausible mechanism to explain the presence of chronic abdominal pain, a cardinal IBS symptom.

PMID: 12864964 [PubMed - indexed for MEDLINE]

National Digestive Diseases Information Clearinghouse (NDDIC)

Irritable Bowel Syndrome

On this page:

What is irritable bowel syndrome (IBS)?

Irritable bowel syndrome is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea. IBS causes a great deal of discomfort and distress, but it does not permanently harm the intestines and does not lead to a serious disease, such as cancer. Most people can control their symptoms with diet, stress management, and prescribed medications. For some people, however, IBS can be disabling. They may be unable to work, attend social events, or even travel short distances.

As many as 20 percent of the adult population, or one in five Americans, have symptoms of IBS, making it one of the most common disorders diagnosed by doctors. It occurs more often in women than in men, and it begins before the age of 35 in about 50 percent of people.

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What are the symptoms of IBS?

Abdominal pain, bloating, and discomfort are the main symptoms of IBS. However, symptoms can vary from person to person. Some people have constipation, which means hard, difficult-to-pass, or infrequent bowel movements. Often these people report straining and cramping when trying to have a bowel movement but cannot eliminate any stool, or they are able to eliminate only a small amount. If they are able to have a bowel movement, there may be mucus in it, which is a fluid that moistens and protect passages in the digestive system. Some people with IBS experience diarrhea, which is frequent, loose, watery, stools. People with diarrhea frequently feel an urgent and uncontrollable need to have a bowel movement. Other people with IBS alternate between constipation and diarrhea. Sometimes people find that their symptoms subside for a few months and then return, while others report a constant worsening of symptoms over time.

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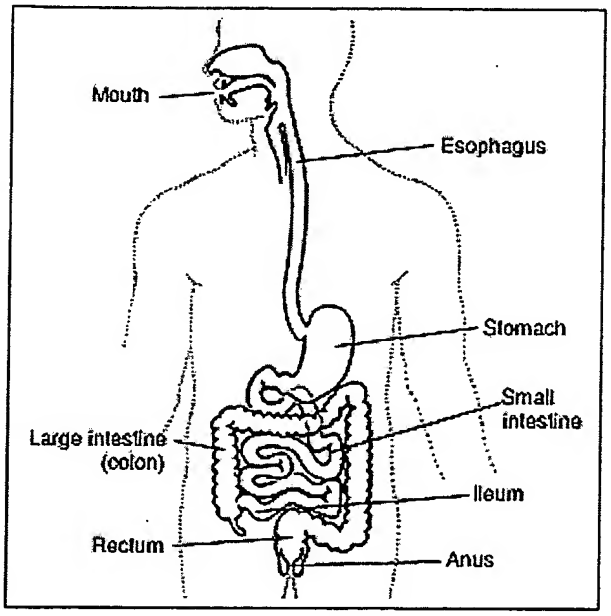
What causes IBS?

Researchers have yet to discover any specific cause for IBS. One theory is that people who suffer from IBS have a colon, or large intestine, that is particularly sensitive and reactive to certain foods and stress. The immune system, which fights infection, may also be involved.



- Normal motility, or movement, may not be present in the colon of a person who has IBS. It can be spasmodic or can even stop working temporarily. Spasms are sudden strong muscle contractions that come and go.
- The lining of the colon called the epithelium, which is affected by the immune and nervous systems, regulates the flow of fluids in and out of the colon. In IBS, the epithelium appears to work properly. However, when the contents inside the colon move too quickly, the colon loses its ability to absorb fluids. The result is too much fluid in the stool. In other people, the movement inside the colon is too slow, which causes extra fluid to be absorbed. As a result, a person develops constipation.
- A person's colon may respond strongly to stimuli such as certain foods or stress that would not bother most people.
- Recent research has reported that serotonin is linked with normal gastrointestinal (GI) functioning. Serotonin is a neurotransmitter, or chemical, that delivers messages from one part of your body to another. Ninety-five percent of the serotonin in your body is located in the GI tract, and the other 5 percent is found in the brain. Cells that line the inside of the bowel work as transporters and carry the serotonin out of the GI tract. People with IBS, however, have diminished receptor activity, causing abnormal levels of serotonin to exist in the GI tract. As a result, they experience problems with bowel movement, motility, and sensation—having more sensitive pain receptors in their GI tract.
- Researchers have reported that IBS may be caused by a bacterial infection in the gastrointestinal tract. Studies show that people who have had gastroenteritis sometimes develop IBS, otherwise called post-infectious IBS.
- Researchers have also found very mild celiac disease in some people with symptoms similar to IBS. People with celiac disease cannot digest gluten, a substance found in wheat, rye, and barley.

People with celiac disease cannot eat these foods without becoming very sick because their immune system responds by damaging the small intestine. A blood test can determine whether celiac disease may be present. (For information about celiac disease, see the NIDDK's Celiac Disease fact sheet.)

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How is IBS diagnosed?

If you think you have IBS, seeing your doctor is the first step. IBS is generally diagnosed on the basis of a complete medical history that includes a careful description of symptoms and a physical examination.

There is no specific test for IBS, although diagnostic tests may be performed to rule out other problems. These tests may include stool sample testing, blood tests, and x rays. Typically, a doctor will perform a sigmoidoscopy, or colonoscopy, which allows the doctor to look inside the colon. This is done by inserting a small, flexible tube with a camera on the end of it through the anus. The camera then transfers the images of your colon onto a large screen for the doctor to see better.

If your test results are negative, the doctor may diagnose IBS based on your symptoms, including how often you have had abdominal pain or discomfort during the past year, when the pain starts and stops in relation to bowel function, and how your bowel frequency and stool consistency have changed. Many doctors refer to a list of specific symptoms that must be present to make a diagnosis of IBS.

Symptoms include

- Abdominal pain or discomfort for at least 12 weeks out of the previous 12 months. These 12 weeks do not have to be consecutive.
- The abdominal pain or discomfort has two of the following three features:
    - It is relieved by having a bowel movement.
    - When it starts, there is a change in how often you have a bowel movement.
    - When it starts, there is a change in the form of the stool or the way it looks.
- Certain symptoms must also be present, such as
    - a change in frequency of bowel movements
    - a change in appearance of bowel movements
    - feelings of uncontrollable urgency to have a bowel movement
    - difficulty or inability to pass stool
    - mucus in the stool
    - bloating
- Bleeding, fever, weight loss, and persistent severe pain are not symptoms of IBS and may indicate other problems such as inflammation, or rarely, cancer.

The following have been associated with a worsening of IBS symptoms

- large meals
- bloating from gas in the colon
- medicines
- wheat, rye, barley, chocolate, milk products, or alcohol
- drinks with caffeine, such as coffee, tea, or colas
- stress, conflict, or emotional upsets

Researchers have found that women with IBS may have more symptoms during their menstrual periods,

suggesting that reproductive hormones can worsen IBS problems.

In addition, people with IBS frequently suffer from depression and anxiety, which can worsen symptoms. Similarly, the symptoms associated with IBS can cause a person to feel depressed and anxious.

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What is the treatment for IBS?

Unfortunately, many people suffer from IBS for a long time before seeking medical treatment. Up to 70 percent of people suffering from IBS are not receiving medical care for their symptoms. No cure has been found for IBS, but many options are available to treat the symptoms. Your doctor will give you the best treatments for your particular symptoms and encourage you to manage stress and make changes to your diet.

Medications are an important part of relieving symptoms. Your doctor may suggest fiber supplements or laxatives for constipation or medicines to decrease diarrhea, such as Lomotil or loperamide (Imodium). An antispasmodic is commonly prescribed, which helps to control colon muscle spasms and reduce abdominal pain. Antidepressants may relieve some symptoms. However, both antispasmodics and antidepressants can worsen constipation, so some doctors will also prescribe medications that relax muscles in the bladder and intestines, such as Donnapine and Librax. These medications contain a mild sedative, which can be habit forming, so they need to be used under the guidance of a physician.

A medication available specifically to treat IBS is alosetron hydrochloride (Lotronex). Lotronex has been reapproved with significant restrictions by the U.S. Food and Drug Administration (FDA) for women with severe IBS who have not responded to conventional therapy and whose primary symptom is diarrhea. However, even in these patients, Lotronex should be used with great caution because it can have serious side effects such as severe constipation or decreased blood flow to the colon.

With any medication, even over-the-counter medications such as laxatives and fiber supplements, it is important to follow your doctor's instructions. Some people report a worsening in abdominal bloating and gas from increased fiber intake, and laxatives can be habit forming if they are used too frequently.

Medications affect people differently, and no one medication or combination of medications will work for everyone with IBS. You will need to work with your doctor to find the best combination of medicine, diet, counseling, and support to control your symptoms.

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How does stress affect IBS?

Stress—feeling mentally or emotionally tense, troubled, angry, or overwhelmed—can stimulate colon spasms in people with IBS. The colon has many nerves that connect it to the brain. Like the heart and the lungs, the colon is partly controlled by the autonomic nervous system, which responds to stress. These nerves control the normal contractions of the colon and cause abdominal discomfort at stressful times. People often experience cramps or "butterflies" when they are nervous or upset. In people with IBS, the colon can be overly responsive to even slight conflict or stress. Stress makes the mind more aware of the sensations that arise in the colon, making the person perceive these sensations as unpleasant.

Some evidence suggests that IBS is affected by the immune system, which fights infection in the body. The immune system is affected by stress. For all these reasons, stress management is an important part of treatment for IBS. Stress management options include

- stress reduction (relaxation) training and relaxation therapies such as meditation
- counseling and support
- regular exercise such as walking or yoga
- changes to the stressful situations in your life

- adequate sleep

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What does the colon do?

The colon, which is about 5 feet long, connects the small intestine to the rectum and anus. The major function of the colon is to absorb water, nutrients, and salts from the partially digested food that enters from the small intestine. Two pints of liquid matter enter the colon from the small intestine each day. Stool volume is a third of a pint. The difference between the amount of fluid entering the colon from the small intestine and the amount of stool in the colon is what the colon absorbs each day.

Colon motility—the contraction of the colon muscles and the movement of its contents—is controlled by nerves, hormones, and impulses in the colon muscles. These contractions move the contents inside the colon toward the rectum. During this passage, water and nutrients are absorbed into the body, and what is left over is stool. A few times each day contractions push the stool down the colon, resulting in a bowel movement. However, if the muscles of the colon, sphincters, and pelvis do not contract in the right way, the contents inside the colon do not move correctly, resulting in abdominal pain, cramps, constipation, a sense of incomplete stool movement, or diarrhea.

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Can changes in diet help IBS?

For many people, careful eating reduces IBS symptoms. Before changing your diet, keep a journal noting the foods that seem to cause distress. Then discuss your findings with your doctor. You may want to consult a registered dietitian who can help you make changes to your diet. For instance, if dairy products cause your symptoms to flare up, you can try eating less of those foods. You might be able to tolerate yogurt better than other dairy products because it contains bacteria that supply the enzyme needed to digest lactose, the sugar found in milk products. Dairy products are an important source of calcium and other nutrients. If you need to avoid dairy products, be sure to get adequate nutrients in the foods you substitute, or take supplements.

In many cases, dietary fiber may lessen IBS symptoms, particularly constipation. However, it may not help with lowering pain or decreasing diarrhea. Whole grain breads and cereals, fruits, and vegetables are good sources of fiber. High-fiber diets keep the colon mildly distended, which may help prevent spasms. Some forms of fiber keep water in the stool, thereby preventing hard stools that are difficult to pass. Doctors usually recommend a diet with enough fiber to produce soft, painless bowel movements. High-fiber diets may cause gas and bloating, although some people report that these symptoms go away within a few weeks. (For information about diets for people with celiac disease, please see the NIDDK's Celiac Disease fact sheet.) Increasing fiber intake by 2 to 3 grams per day will help reduce the risk of increased gas and bloating.

Drinking six to eight glasses of plain water a day is important, especially if you have diarrhea. Drinking carbonated beverages, such as sodas, may result in gas and cause discomfort. Chewing gum and eating too quickly can lead to swallowing air, which also leads to gas.

Large meals can cause cramping and diarrhea, so eating smaller meals more often, or eating smaller portions, may help IBS symptoms. Eating meals that are low in fat and high in carbohydrates such as pasta, rice, whole-grain breads and cereals (unless you have celiac disease), fruits, and vegetables may help.

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Is IBS linked to other health problems?

As its name indicates, IBS is a syndrome—a combination of signs and symptoms. IBS has not been

shown to lead to a serious disease, including cancer. Through the years, IBS has been called by many names, among them colitis, mucous colitis, spastic colon, or spastic bowel. However, no link has been established between IBS and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis.

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Points to Remember

- IBS is a disorder that interferes with the normal functions of the colon. The symptoms are crampy abdominal pain, bloating, constipation, and diarrhea.
- IBS is a common disorder found more often in women than men.
- People with IBS have colons that are more sensitive and reactive to things that might not bother other people, such as stress, large meals, gas, medicines, certain foods, caffeine, or alcohol.
- IBS is diagnosed by its signs and symptoms and by the absence of other diseases.
- Most people can control their symptoms by taking medicines such as laxatives, antidiarrhea medicines, antispasmodics, or antidepressants; reducing stress; and changing their diet.
- IBS does not harm the intestines and does not lead to cancer. It is not related to Crohn's disease or ulcerative colitis.

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Hope Through Research

The NIDDK conducts and supports research into many kinds of digestive disorders including IBS. Researchers are studying gastrointestinal motility and sensitivity to find possible treatments for IBS. These studies include the structure and contraction of gastrointestinal muscles, as well as the mechanics of fluid movement through the intestines. Understanding the influence of the nerves, hormones, and inflammation in IBS may lead to new treatments to better control the symptoms.

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For More Information

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The National Digestive Diseases Information Clearinghouse collects resource information about

digestive diseases for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Reference Collection. This database provides titles, abstracts, and availability information for health information and health education resources. The NIDDK Reference Collection is a service of the National Institutes of Health.

You may view the results of the automatic search on irritable bowel syndrome.

If you wish to perform your own search of the database, you may access and search the NIDDK Reference Collection database online.

This publication may contain information about medications used to treat a health condition. When this publication was prepared, the NIDDK included the most current information available. Occasionally, new information about medication is released. For updates or for questions about any medications, please contact the U.S. Food and Drug Administration at 1–888–INFO–FDA (463–6332), a tollfree call, or visit their website at www.fda.gov. Consult your doctor for more information.

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The National Digestive Diseases Information Clearinghouse (NDDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health of the U.S. Department of Health and Human Services. Established in 1980, the Clearinghouse provides information about digestive diseases to people with digestive disorders and to their families, health care professionals, and the public. The NDDIC answers inquiries, develops and distributes publications, and works closely with professional and patient organizations and Government agencies to coordinate resources about digestive diseases.

Publications produced by the Clearinghouse are carefully reviewed by both NIDDK scientists and outside experts.

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1: Chin J Dig Dis. 2005;6(3):122-32.

Irritable bowel syndrome and inflammatory bowel disease: interrelated diseases?

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In the past inflammatory bowel disease (IBD), celiac disease and irritable bowel syndrome (IBS) were regarded as completely separate disorders. Now, with the description of inflammation, albeit low-grade, in IBS, and of symptom overlap between IBS and celiac disease, this contention has come under question. Is there true overlap between these disorders? Despite the limitations of available data one cannot but be struck by some areas of apparent convergence: IBD and celiac disease in remission, lymphocytic colitis and microscopic inflammation in IBS, in general, and, especially, in the post-infectious IBS category. The convergence between latent celiac disease and sub-clinical IBD, on the one hand, and IBS, on the other, appears, based on available evidence, to be somewhat spurious and may largely relate to misdiagnosis, a phenomenon which may also explain the apparent evolution of IBS into IBD in some studies. Similarities between IBS and lymphocytic colitis are more striking and less readily dismissed; as for IBS, well documented instances of progression of lymphocytic colitis to full-blown IBD are infrequent, suggesting a true separation between this disorder and classical IBD. Do IBS and lymphocytic colitis represent different responses to similar triggers? Will some of the 'inflamed' IBS subgroup be reclassified as part of the spectrum of lymphocytic colitis in the future? Will inflammation emerge as a common underlying factor in the pathogenesis of IBS? The answer to these and many questions must await further study of this fascinating area.

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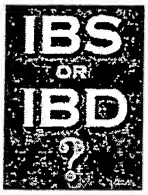
IBS and IBD: Two Very Different Disorders



Many people are confused about two distinct gastrointestinal disorders -- IBD and IBS. Different intestinal disorders can produce similar symptoms. *Irritable bowel syndrome* (IBS) is a condition that produces some symptoms similar to those of *inflammatory bowel disease* (IBD), but they are not the same condition, and they involve very different treatments. Therefore, getting an accurate diagnosis is essential to managing your condition properly. The following Q&A will give you an overview of IBS and how it differs from IBD.

Irritable bowel syndrome (IBS) is classified as a *functional* gastrointestinal disorder, which means there is some type of disturbance in bowel function. It is not a disease, but rather a *syndrome*, defined as a group of symptoms. These typically include chronic abdominal pain or discomfort and diarrhea, constipation, or alternating bouts of the two. People with IBS are also more likely to have other functional disorders such as fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, and temporomandibular joint (TMJ) disorder.

IBS has been referred to by many names, including mucous colitis and spastic colitis, but these terms are inaccurate and lead to confusion about what IBS is. While the word "colitis" refers to an inflammation of the colon (large intestine), IBS does not cause inflammation. Unlike ulcerative colitis patients, IBS sufferers show no sign of disease or abnormalities when the colon is examined.

IBS does not produce the destructive inflammation found in IBD, so in many respects it is a less serious condition. It doesn't result in permanent harm to the intestines, intestinal bleeding, or the harmful complications often occurring with IBD. People with IBS are not at higher risk for colon cancer, nor are they more likely to develop IBD or other gastrointestinal diseases. IBS seldom requires hospitalization, and treatment does not usually involve surgery or powerful medications, such as steroids or immunosuppressives.

IBS can, however, cause a great deal of discomfort and distress, and can severely affect an individual's quality of life. Its symptoms can range from mildly annoying to disabling -- impinging on a person's self-image, social life, and ability to work or travel. People with IBS are more likely to seek health care for both gastrointestinal and non-gastrointestinal complaints compared to people without IBS. It is estimated that IBS results in direct and indirect medical costs of over $20 billion annually.

Who Gets IBS?

According to the International Foundation for Functional Gastrointestinal Disorders (www.iffgd.org), IBS affects at least 10% to 20% of adults in the U.S. -- mostly women -- and is second only to the common cold as a cause of absenteeism from work. It is the disorder most commonly diagnosed by gastroenterologists and one of the top ten most frequently diagnosed conditions among U.S. physicians. IBS usually begins in late adolescence or early adult life -- most often at times of emotional stress.

X. RELATED PROCEEDINGS APPENDIX

None